REMARKS/ARGUMENTS

Applicants acknowledge receipt of the Office Action dated June 5, 2008. Claims 1, 4, and 6-11 are pending in the application. Claims 1, 4, and 6-11 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,455,298 ("*McFarlane*") in view of U.S. Patent No. 5,707,673 ("*Prevost*"), and WO 00/23546 ("*Beaudoin*"). Applicants believe all pending claims are allowable over the art of record and respectfully request reconsideration and allowance of all claims.

I. OBJECTION TO CLAIMS 1 AND 4

Applicants have amended claims 1 and 4 as suggested in the Office Action. Thus, Applicants respectfully request that the objection to those claims be withdraw.

II. REJECTIONS UNDER 35 U.S.C. §103

Claims 1, 4 and 6-11 have been rejected as unpatentable over *McFarlane* in view of *Prevost* and *Beaudoin.*

McFarlane is cited as disclosing a process for the extraction of lipids from Perna canaliculus solids using ethyl acetate. The organic solvent is dried before being evaporated. *McFarlane* fails to teach nanofiltration of the solvent extract.

Prevost is cited as disclosing a process for extracting lipids in accordance with claim 1 except that it does not teach the use of a solvent selected from acetone, hexane and ethyl acetate. *Prevost* actually teaches as solvent the use of propane or more generally "liquefied solvent" (col. 3, lines 46-59).

According to the Office Action, *Prevost* teaches (column 2, line 1) that hexane was the most commonly used solvent prior to the invention of *Prevost.* However, that prior use of hexane was not said to be in a process of the kind described by *Prevost.*

Far from suggesting that one should use any of the now claimed solvents, *Prevost* teaches the use of propane or more generally "liquefied solvent" (col. 3, lines 46-59). It specifically teaches against the use of hexane (col. 2, lines 46-51) and says nothing about acetone or ethyl acetate. It is strongly teaching away from normally liquid solvents and it teaches instead solvents liquefied by pressure.

Beaudoin is cited for disclosing acetone and ethyl acetate to extract lipid material from marine and aquatic animals.

With regard to claim 1, the Office Action fails to state how or why a person of ordinary skill would combine these teachings to reach something claimed. The rejection is purely conclusory. The Office Action merely states that the references are good not only for what they teach, but for what a skilled person would reasonably infer. However, the Office Action does not state what a skilled person of ordinary skill in the art is supposed to reasonably infer from any of these teachings.

Applicants are unclear how the teaching from *Beaudoin* forms part of the objection. *McFarlane* is cited as showing extraction using ethyl acetate. All that is said of *Beaudoin* is that it too uses ethyl acetate and also acetone. Since claim 1 does not require the use of both ethyl acetate and acetone, it is unclear why *Beaudoin* is involved in the objection.

Since *Beaudoin* is relied upon in relation to the rejection of claim 1, it is reasonable and logical to suppose that the combination of *McFarlane* and *Prevost* is not considered sufficient in itself to support the objection (with which Applicants concur). Absent identification of some teaching in *Beaudoin* that contributes something not seen in *McFarlane* and *Prevost* in combination, it is clear that the combination of the three references equally cannot then be a sufficient basis for rejection.

Looking in more detail at the combination of *McFarlane* and *Prevost* and surmising that the objection based on those is that it would be obvious to supplement the extraction method of *McFarlane* using ethyl acetate by nanofiltration of the extract because nanofiltration is taught in *Prevost*, Applicants submit that it was not the case that adding nanofiltration to the process of *McFarlane* was obvious.

Prevost makes it clear why nanofiltration is used and it is a reason that does not carry over to or have relevance to the *McFarlane* process. Thus, *Prevost* teaches the use of a normally gaseous material in liquefied form as solvent. If this is to be evaporated to remove it from the solvent extract, it cannot be reused without being re-liquefied. The liquefaction is a process that will consume considerable energy of compression, which will be essentially wasted (col. 3, lines 14). *Prevost* reduces this energy cost incurred by evaporating and then compressing to re-liquefy the solvent by reducing the amount of solvent that has to be removed by evaporation.

The solvent that is removed in a liquid state by nanofiltration can be recycled without having to be converted from the gaseous state to the liquid state by compression.

Nanofiltration is not however an energy free process. Pressurization of the solvent extract is needed to drive the nanofiltration process. For *Prevost*, this is outweighed by the energy saving of avoiding the gas to liquid conversion.

No such considerations apply in *McFarlane* however. There, the ethyl acetate removed by evaporation can be liquefied simply by allowing it to condense and heat can be recovered from that condensation. No energy input is required for the gas to liquid transition, so none can be saved by nanofiltration. On the other hand, extra energy would still be required to drive the nanofiltration. Accordingly, a person of ordinary skill in the art would see that nanofiltration would not provide in *McFarlane* the benefit for which it is suggested in *Prevost*. The combination suggested by the Office Action is therefore in reality simply based on hindsight, which is impermissible. *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364-1365 (Fed. Cir. 2008); *Crown Operations Intern., Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1376 (Fed. Cir. 2002). *Beaudoin* contributes nothing further to the issue.

The purpose for which nanofiltration is used in the invention is quite different to that for which it is suggested in *Prevost* and is not taught in the art. As discussed in Applicants' February 6th response, the use of nanofiltration has been found to make a profound and entirely unpredictable beneficial alteration in the make up and utility of the resulting extract.

As demonstrated in the present application, the methods taught in the application provide a much higher level of polyunsaturated free fatty acids (PUFAs) than are achieved according to *McFarlane*. For instance, Example 1 shows a level of PUFA of 15.7%, whereas *McFarlane* in the table at column 2 shows a total lipid content of only 10.54% at most and an average lipid level of only 9.09%. Clearly, the total lipid yield in the Applicants' process would necessarily be in excess of the yield of PUFA, so when compared to *McFarlane*, the increase would be even more striking. Even on the basis of comparing PUFA with total lipid, it is still a 73% improvement.

No such likely benefit is deducible from *Prevost*.

The unexpected advantage conferred by the invention goes beyond merely the total quantity of PUFA obtained. As discussed in the February 6th response, the invented process has

been found to produce a product having superior clinical performance by virtue of the balance of components in the extract.

The balance of components in the lipid extract is of course due not just to the starting material or to the solvent, but to the interaction of the two and the conditions used. Thus, the particular result of using the stipulated solvents under the stipulated conditions was far from predictable, whether from *McFarlane*, or *Prevost*, or *Beaudoin*, alone or in combination.

Applicants' aim is not just to obtain some extraction of lipids but to obtain a balance of extracted lipids from Perna canaliculus that is optimised compared to what has previously been achieved.

Applicants filed previously a copy of an article in European Companion Animal Health in 2006 authored with others by one of the present inventors. Another copy is attached as Exhibit 1 for convenience. This compares *inter alia* the anti-inflammatory activity of SuPernol and BionoVex, the first being an acetone extract of green lipped mussel prepared without nanofiltration, but using vacuum evaporation for solvent removal, and the second being a product obtained by a process according to an embodiment of the invention (see Fig 4). It can be seen that the BionoVex product is superior. This may be due to the removal by nanofiltration of certain small molecules extracted by the solvent which pass through the filtration membrane. No such advantage is hinted at in *Prevost,* where the permeate is described as being "substantially extractive free" (col. 3, last line).

The Office Action states that claims 8-11 are obvious absent a showing of unexpected results. However, just as such a showing would be relevant to those claims, it is relevant to claims 1 and 4, and 6 and 7 also. Furthermore, the results set out in Exhibit 1 clearly demonstrate further unexpected benefits over and above the yield figures discussed above.

Applicants respectfully submit that all of the objections under §103 should be withdrawn, which action is respectfully requested.

III. CONCLUSION

If any fees are inadvertently omitted or if any additional fees are required or have been overpaid, please appropriately charge or credit those fees to Conley Rose, P.C. Deposit Account Number 03-2769.

Respectfully submitted,

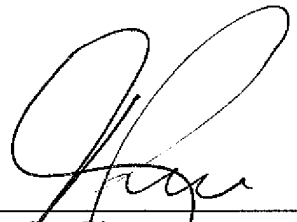

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EXHIBIT 1

Polyunsaturated Fatty Acids – Are They Alternative Anti-inflammatories?

a report by
Richard Geering[1], Clare Engelke[2] *and* Tony Chandler[3]

1. Lecturer, Imperial College London 2. Research Associate, Writtle College, Essex
3. Managing Director, Bionovate Ltd.

Polyunsaturated fatty acids (PUFAs) have been associated with wide-ranging benefits for many years including cardiovascular disease and inflammatory conditions. Clinically, however, PUFAs have limited effect at standard dosages.

Potent PUFAs have recently been discovered in extracts from green lipped mussels (GLM, *Perna canaliculus*) that are 300 times more effective than eicosapentaenoic acid (EPA) and demonstrate significant anti-inflammatory activity. PUFAs are heat-labile compounds that are easily denatured particularly during processing or freeze-drying. The method of production substantially influences the characteristics of the lipids and new techniques have been developed over the last year that significantly improve the yield and performance of these fatty acids.

The availability of the new lipid extracts has been incorporated into a number of unique and innovative new products to further help veterinary joint-care management.

Polyunsaturated fatty acids (PUFAs) are found in both plant and animal sources and by definition must have more than two double bonds. The position of the first double bond dictates much about the structural properties of the PUFA and typically these are described as omega-3, omega-6 etc.

PUFAs are the obligate precursors of a wide range of signalling molecules, including the eicosanoids, which have a central role in inflammatory responses. Furthermore, it is now becoming increasingly evident that in many disease states (obesity, diabetes, dental disorders and joint disease for example) low-grade inflammation exists which has serious implications for all systems.

Their roles in physiological and pathophysiological situations are many and diverse quite apart from storage and structural functions. Recently, Serhan and others have discovered novel eicosanoids molecules (resolvins – lipoxin etc) with roles in controlling and switching off inflammation, which have exciting possibilities, as well as dietary and nutraceutical implications.

Eicosanoids are 20-carbon compounds derived from PUFAs, known as the eicosaenoic acids and which serve as precursors to a variety of other biologically active compounds in cell signalling. These include prostaglandins, thromboxanes and leukotrienes that are themselves eicosanoids.

At the cellular level, arachidonic acid is itself an eicosanoid and is one of the major sources of 20-carbon structures that provide the essential precursors of prostaglandins (sometimes referred to as prostanoids), thromboxanes and leukotrienes. These compounds act as biological regulators within animals and their function depends upon the type of tissue and relevant enzyme systems involved and are well known mediators of inflammation and immune responses.[1]

Thus, effects of altering dietary PUFA composition have a considerable influence on the inflammatory response through alterations in the type and relative quantities of eicosanoids synthesised. Omega-3 PUFAs inhibit the conversion of the precursor lipid, arachadonic acid by the lipoxygenase and cyclo-oxygenase pathways, to proinflammatory metabolites such as leukotriene B4, 5-hydroxyeicosopentaenoic acid and thromboxane A2.

In general, the two-series prostaglandins (derived from omega-6 PUFAs) are far more proinflammatory than the three-series prostaglandins (derived from omega-3 PUFAs).

The leukocytes from many marine animals and some freshwater fish are high in omega-3 fatty acids and make leukotrienes and lipoxins from both arachadonic acid (C20:4) and eicosapentaenoic acid (EPA) (C20:5). The immune functions of these products are similar to those in mammals, but fish generate both four- and five-series leukotrienes and lipoxins compared to mammals using predominately C20:4.[2]

Richard Geering is a Veterinary Surgeon with 30 years in equine veterinary practice. He has been a lecturer in equine and animal sciences and is currently at Imperial College where his main interest is inflammation in man and animals with particular reference to dietary and marine lipids.

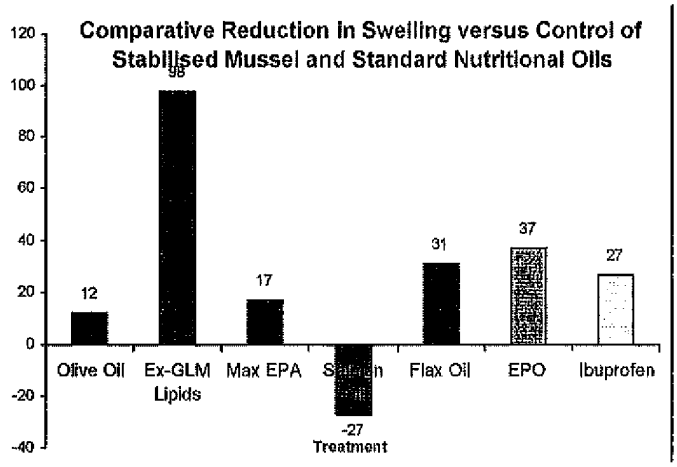
Clare Engelke completed a Bachelor of Science in Agriculture at the University of Western Australia (UWA) followed by a PhD in microbiology/biochemistry, in conjunction with CSIRO Livestock Industries. Her PhD research focussed on the formation of conjugated linoleic acids in kangaroos and ruminants. Clare is presently a research associate at Writtle College, Essex.

Tony Chandler is a Biological Chemist with a pharmaceutical career, which began in 1981. More recently, Tony has been the MD of Bionovate Ltd who specialise in the development of novel and innovative procedures and products for the benefit of human and animal health.

Table 1

	Product 1	Product 2	Product 3
	High quality mussels, cold proprietary dried	High quality mussels, cooked and proprietary dried	Low quality mussels, cooked and freeze dried
Fat (Acid Hydrolysis) g/100g	*8.2*	*8*	*5.4*
C18.4 Octadecatetraenoic acid	*2.5*	*1.7*	*0.7*
C20.4 Eicosatetraenoic acid (omega-3)	*0.5*	*0.2*	*0.1*
C20.5 Eicosatetraenoic acid	*19*	*12.3*	*4.8*
C22.6 Docosahexaenoic acid	*11.4*	*8.4*	*3.3*
Total	***41.6***	***30.6***	***14.3***

Figure 1



Increases in the proportion of n-3 and decreases in n-6 PUFA precursors in the body should therefore show significant reduction in inflammatory effect. The lipooxygenases have a greater affinity for n-3 PUFAs than n-6 PUFAs and thus produce a greater proportion of five-series leukotrienes. The five-series leukotrienes are much less biologically potent compared with the four-series leukotrienes. The benefits of this are far-reaching as a means for minimising arthritis without the need for drug intervention.

The advantages of using omega-3 PUFAs to inhibit arachadonic acid metabolism is that unlike most commonly used anti-inflammatory drugs, they do not completely block cyclooxygenase activity, thus allowing for synthesis of beneficial eicosanoids such as prostacyclin and prostaglandin E2. A further advantage over the more commonly used non-steroidal anti-inflammatory drugs is the absence of adverse gastric, renal and cardiac effects.[3]

The most recognised naturally occurring eicosanoids are found in marine-derived oils such as fish oils that contain the omega-3 series of PUFAs. Fish oil is a well-known source of one such eicosanoid in particular, namely EPA. EPA has been used for many years with little if any clinical anti-inflammatory activity at the standard dose.[4]

The anti-inflammatory activity of natural PUFAs has been evaluated using the rat-paw oedema test. This test allows comparative oral activity of compounds to be evaluated (see *Figure 1*).[4]

The supercritical CO_2 extracted lipids (Lyprinol) from green lipped mussel (GLM; *Perna canaliculus*) show far greater anti-inflammatory activity than EPA with some 300-times more potency.[4]

These results first confirmed that the lipids from cold processed GLM exhibit considerable anti-inflammatory activity.[5,6] This activity has been confirmed in human trials and pharmacological studies.[4,6]

Earlier attempts to evaluate the efficacy of GLM lipids were hampered by the effect of manufacturing and processing methods on their activity. Original methods heated the material, either by cooking in steam or by various drying methods used to produce the original powdered material. However, heat denatures the important omega-3 series eicosanoid structures which reduces their anti-inflammatory activity (see *Table 1* and *Figure 2*).

The Effect Of Processing Upon Fatty Acid Composition of Green Lipped Mussel

Different processing methods have been compared for fatty acid profiles.

- Product 1 high-quality cold mussels premium processed.
- Product 2 high-quality cooked mussels premium processed.
- Product 3 low-quality cooked mussels freeze-dried.

Cold premium processing retains greater proportions of long-chain PUFAs that contribute to

the potent anti-inflammatory activity of the GLM lipids. To confirm that the fatty acid profiles are reflected in the anti-inflammatory activity of the products they were subsequently assayed in a neutrophil superoxidase test. The activity of the cold processed vs the cooked and freeze-dried material was compared using a superoxide assay as an inflammatory marker. Aspirin was used as a positive control.

Product 1 (SuPerna™, Bionovate Ltd) has subsequently demonstrated greater anti-inflammatory activity than Product 3, a commercially available freeze-dried product. The anti-inflammatory effect is also greater than that of the equivalent concentration of aspirin.

Having developed a method of processing GLM to produce a high level of active lipid content the opportunity to evaluate these lipids was made possible. Two lipid extracts have been developed (SuPernol™ and BionoVex™, Bionovate td) and their anti-inflammatory activity compared in nitric oxide and superoxidase assays (see *Figure 3*).

The concentration required to produce 50% inhibition in the assay was 0.6ug/ml confirming the high potency of BionoVex (data on file).

In a different assay using neutrophil superoxide production the anti-inflammatory activity has been compared for a number of extracted materials (see *Figure 4*).

The range of PUFAs found in cold processed extracts of GLM have demonstrated potent anti-inflammatory activity with no discernable side effects despite many years of use in thousands of people and dogs. The eicosatetraenoic acids (20C ETAs), which are structurally similar to arachidonic acid but of the omega-3 series, may act as arachidonic acid anti-metabolites and therefore down-regulate the excessive metabolism of arachidonic acid by cyclooxygenase or lipoxygenase, hence reducing the inflammatory flux that produces prostaglandins and leukotrienes, respectively. Alternatively, they may act on the release of membrane-bound arachidonic acid by phospho-lipase A2 inhibition or by down-regulating the transcription of enzymes from the nucleus. Finally, there may be a PUFA or PUFAs in the lipid extracts that act as precursors for lipoxin production. Lipoxins are highly potent structures acting as the body's own anti-inflammatories and have increas-ingly come into the spotlight on recent years.[2]

Figure 2: Comparative Anti-inflammatory Activity

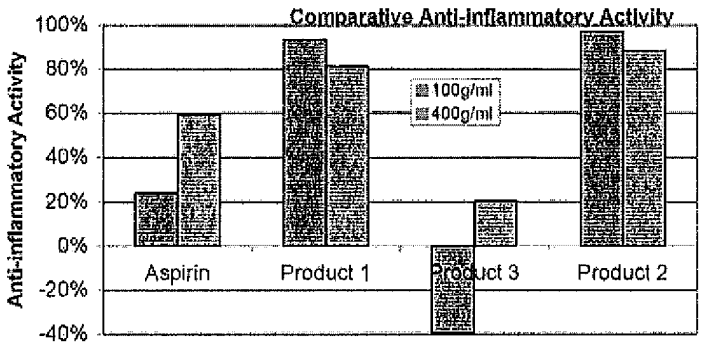


Figure 3: RAW 264.7 Cells Challenged with 1µg/ml LPS and Treated with BionoVex Lipid Extract

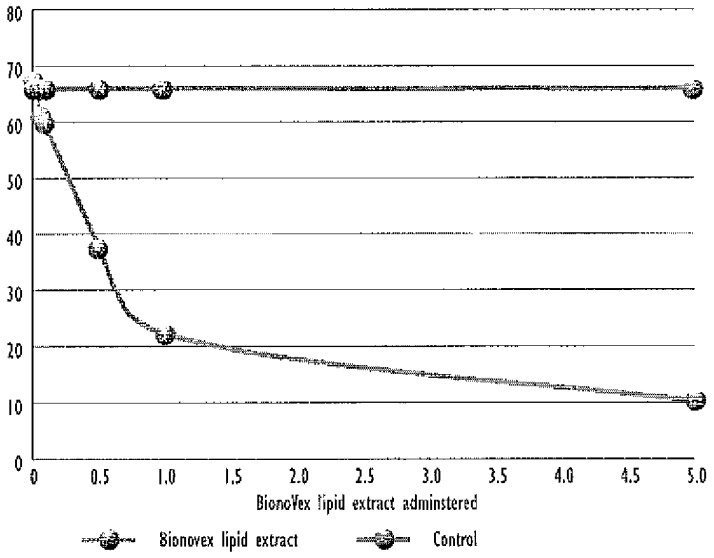
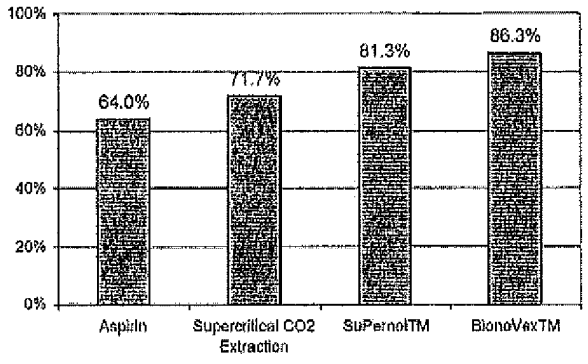


Figure 4: Comprative Anti-inflammatory Activity of GLM Lipid Extract



This mechanism of action is clearly different to classical enzyme-drug interaction that produces rapid and potent inhibition. ETAs as anti-metabolites, however, act more slowly over three to ten days and exert their effect in chronic inflammatory conditions.

Figure 5: The Effect of Lipids on Decrease Lameness Score

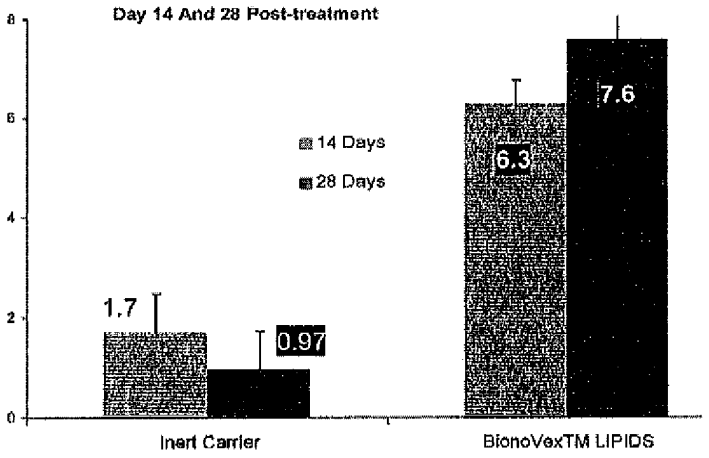


Figure 6

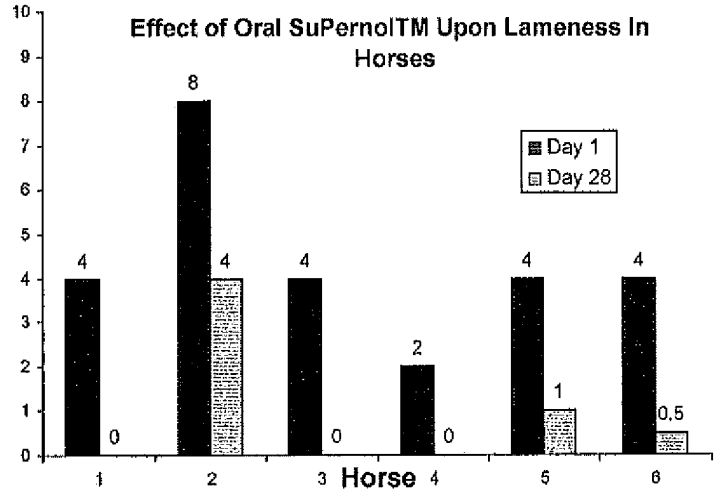
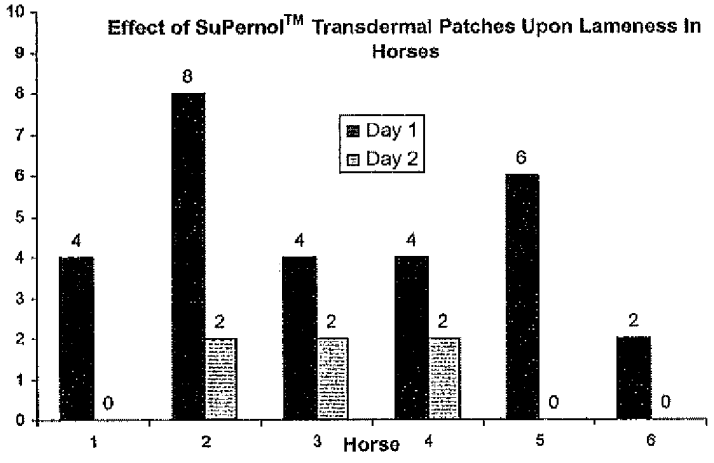


Figure 7



The potent anti-inflammatory action of SuPernol and BionoVex has been confirmed in veterinary studies (see *Figure 5*).[5]

A double-blind, randomised crossover study at Imperial College London evaluated the effect of BionoVex on arthritis in horses. A dose of 200mg per day was administered and animals were assessed by clinical examinations, including flexion tests and gait analysis. Within 14 days, BionoVex demonstrated a significant improvement in lameness (data on file).

The efficacy of SuPernol in equine lameness has also been confirmed at lower dosages. Although using small numbers, three of the horses were sound (score=0). All horses improved within the 28-day period (see *Figure 6*).

Having demonstrated highly effective activity orally, SuPernol was further evaluated in a transdermal patch. SuPernol was combined with two formats of hyaluronic acid and menthol into hydrogel on a felt backing (EquiSustain Patch, Iceni UK). These patches were applied directly to the horses joint and bandaged to keep in place. The patch is designed to be effective for more than 24 hours. The patch works rapidly and has been patented.

The evaluation included flexion testing by veterinary assessment and gait analysis using SIMI Motion software (Germany) to determine the effect of the patch upon joint movement and stride characteristics over 24 hours. All horses were confirmed as lame and re-assessed at day one of the trial. All tests were repeated at day two of the trial, following 24 hours of bandaging with the patch.

For gait analysis with SIMI software, the point of rotation at each joint and centre of mass on the horse is marked with visible dots. The horse then trotted past a five metre video analysis set-up and recorded. In the patch trial, this was repeated ten times and in both directions.

For analysis of gait before and after the patches, the SIMI programme was used to determine differences in stride length, tracking distance and diagonal stride distance before and after the bandaging period.

The joint markers were connected to compare the range of movement in the bandaged joints on day one and day two of the trial (see *Figure 7*).

The use of SIMI allows an objective assessment of joint mobility and stride characteristics, which can be expressed graphically to demonstrate changes in joint angle and movement.

The SIMI analysis confirmed the results of flexion testing (see *Figure 7*).

All horses improved in 24 hours. Three horses became sound within this period. No adverse skin reaction to the patch was observed.

The patches offer an innovative and unique opportunity in the joint-care management of horses. On those frequent occasions when joints "flare-up" such as in chronic lameness, box or stable accidents, or kicks, immediate and intensive treatment is required at the injured site. The duration of activity of these new patches offers an effective aid in joint care for horses.

The importance of dietary essential fatty acids in eicosanoid metabolism is well founded.[7] As the mechanisms of arachidonic acid metabolism are being unravelled, the influence of naturally occurring eicosanoids, particularly in the areas of leukotriene inhibition, are being elucidated.

The availability of potent natural lipids such as SuPernol and BionoVex due to the improvement in processing technology and extraction will help to provide new products for animal joint-care management.

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